IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application of: Clendennen *et al.*	Confirmation No. 8290
Application No.: 09/811,093	Group Art Unit: 1638
Filing Date: March 16, 2001	Examiner: Mehta, Ashwin D.
For: MELON PROMOTERS FOR EXPRESSION OF TRANSGENES IN PLANTS	Atty. Docket No.: 4257-0025.30

APPELLANT'S BRIEF (37 CFR § 1.192)

Introductory Comments

Applicants appeal the rejections of the final Office Action mailed January 30, 2004, in the captioned application. A Notice of Appeal and a Petition for Extension of Time are filed herewith. Authorization is hereby granted to have any fees required for consideration of this Brief, and any accompanying submission, charged to deposit account no. 50-1108.

Real Party In Interest (§1.192(c)(1))

Exelixis, Inc. is the assignee of the referenced application and the real party in interest. Assignments from the inventors to Exelixis, Inc. have been recorded at the Patent Office (reel 011945, frame 0815; reel 011948, frame 0399).

Related Appeals and Interference (§1.192(c)(2))

No other appeals or interferences are known to appellant, appellant's legal representative, or assignee, that will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

Status of Claims (§1.192(c)(3))

Claims 1, 5, 7, 9-12, 15, and 19-23 are pending; and claims 2-4, 6, 8, 13, 14, and 16-18 have been cancelled. Claim 5 is objected to as being dependent upon a rejected base claim. Claim 5 recites "The isolated nucleic acid molecule of claim 1, wherein the

portion of the nucleotide sequence is nucleotides 156-1708 of SEQ ID NO:42." The remaining pending claims (i.e. 1, 7, 9-12, 15, and 19-23), which are listed in the Appendix, are rejected under 35 USC § 112, 1st paragraph; Applicants appeal this rejection.

Status of Amendments (§1.192(c)(4))

No amendments were filed subsequent to the final rejection.

Summary of the Invention (§1.192(c)(5))

The invention is an isolated nucleic acid molecule that comprises a promoter operably linked to a heterologous protein-encoding polynucleotide sequence. The promoter consists of a portion of the nucleotide sequence presented as SEQ ID NO:42 that directs fruit-associated expression of the protein in a plant cell. A specific embodiment of the invention is covered by claim 5 which recites that the portion of the nucleotide sequence is nucleotides 156-1708 of SEQ ID NO:42. This portion of SEQ ID NO:42 is a segment of genomic DNA that the inventors obtained from cantaloupe (*Cucumis melo*). It is an upstream region of a gene that is abundantly expressed in ripe fruit only (specification, page 24, line 31 to page 25, line 32). The inventors determined that the gene is Mel7, and that the isolated promoter region is sufficient to direct fruit-specific expression of a reporter gene in a variety of ripe fruit including apple, pear, and tomato (specification, page 32, lines 11-42).

Issues (§1.192(c)(6))

The first issue presented for review is whether the claimed subject matter is described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

The second issue presented for review is whether the specification enables those skilled in the art to make and use portions of SEQ ID NO:42, in addition to nucleotides 145-1708, that can direct fruit-associated expression of a heterologous protein in a plant cell.

Grouping of Claims (§1.192(c)(7))

For each ground of rejection, the group of rejected claims stands or falls together.

Argument (§1.192(c)(8))

I. Written description rejection

The examiner has the intial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the original disclosure a description of the invention defined by the claims (Fed. Reg., Vol 66, No. 4, January 5, 2001, p. 1107, citing *Wertheim*, 541 F.2d at 263, 191 USPQ at 97). In the final office action, the Examiner stated: "the previous Office actions provided a proper rejection following the written description guidelines." In the office action mailed October 1, 2003, the Examiner made the following arguments in support of the rejection:

> ... it remains that the claim encompasses any portion size of a 1735 bp sequence, no matter how small, having fruit-associated promoter activity. Yet, the smallest fragment of SEQ ID NO: 42 that is correlated by the specification as having fruit-associated expression consists of bases 156-1708. This single species is not representative of all of the species encompassed by the claims. This single species does not give any information about the sequences within it that, alone would retain the same transcriptional activity.

However, the Examiner never provided reasons or gave evidence as to why persons skilled in the art would not recognize the dislosure as providing an adequate written description of the claimed invention. Thus, Applicants maintain that the Examiner has not satisfied the initial burden of a proper rejection under the written description requirement of 35 U.S.C. §112, 1st paragraph.

The specification defines "promoter" or "promoter segment" as "a sequence of DNA that functions in a promoter disclosed herein to direct transcription of a downstream gene." (p. 7, lines 5-6). Applicants show a single genomic fragment of the Mel7 promoter region, nucleotides 156-1708 of SEQ ID NO: 42, as capable of directing fruit-associated transcription of a downstream gene. Claim 1 encompasses this fragment (when operably linked to a heterologous protein-encoding polynucleotide sequence), as well as subfragments of this genomic fragment that retain the ability to promote fruit-associated expression of the heterologous protein.

The situation here is somewhat analagous to Example 9 in the "Revised Interim Written Description Guidelines Training Materials" published on the USPTO website. In that example, "the claim was drawn to a genus of nucleic acids all of which must hybridize with SEQ ID NO:1 and must encode a protein with a specific activity" (p. 36). Even though only a single species (i.e. SEQ ID NO:1) was disclosed and reduced to practice, it was concluded that the claimed genus was adequately described because:

> A person of skill in the art would not expect substantial variation among species encompassed within the scope of the claims because the highly stringent hybridization conditions set forth in the claim yield structurally similar DNAs. Thus, a representative number of species is disclosed, since highly stringent hybridzation conditions in combination with the coding function of DNA and the level of skill and knowledge in the art are adequate to determine that applicant was in possession of the claimed invention. (see p. 36-37).

If the Examiner were to apply the same arguments being made against Applicants' claims in the present case, to the hypothetical claim of Example 9 of the Training Materials, the Examiner would reach a conclusion that is contrary to the Training Materials – i.e., that the claim lacks adequate written description support because the precise sequences responsible for the functional activity recited in the claim are not disclosed.

In the present case, Applicants' claimed genus is clearly much less-encompassing than the genus encompassed by the claim of Example 9 of Training Materials, because Applicants' genus encompasses only fragments of the disclosed promoter sequence that retain promoter activity – i.e. variant sequences that could hybridize under high stringency conditions are not claimed. Exhibits A-E provided with Applicants amendment mailed 7/22/03 show that promoter deletion analysis was routinely used by those skilled in the art to identify subfragments of a promoter sequence that retain promoter activity. Thus, following the analysis from Example 9 of the Training Materials, claim 1 is supported by adequate written description.

II. Enablement rejection

The Examiner rejected claims 1,7, 9-12, 15, and 19-23, maintaining that the specification enables only the portion of SEQ ID NO: 42 consisting of nucleotides 146-1708 that directs fruit-associated transcription, and does not reasonably provide

enablement for any other portion of SEQ ID NO: 42 as having the functional activity of directing fruit-associated transcription (p. 3, paragraph #5).

At the time of the invention, it was well within the ability of those skilled in the art to take a promoter segment of 1,562 nucleotides, and perform deletion analysis to obtain smaller segments of the same sequence and determine whether they retain promoter activity. This is evidenced by the abstracts submitted as Exhibits A-E with Applicants' amendment dated July 22, 2003. The Examiner seems to want a disclosure of the precise minimal promoter segment necessary for fruit-associated expression because claim 1 "encompasses the minimal promoter fragment that retains this activity" (Final Office Action, p. 4, line 8). However, this is not a requirement of the patent law. In re Wands ((CA FC) 8 USPQ2d 1400) lists eight factors to be considered in determining whether a disclosure would require undue experimentation:

1. Quantity of experimentation necessary. At the time of the invention it was within the capabilities of one of ordinary skill in the art to start with a 1562 nucleotide sequence known to have a certain promoter activity and perform a promoter deletion experiment to determine the portion of the sequence responsible for the promoter activity. This is evidenced by Exhibits A-E submitted with Applicants' amendment filed July 22, 2003. Thus, the quantity of experimentation needed to practice the scope of the invention recited in claim 1 is minimal.

In a previous office action, the Examiner implied that the need to conduct <u>any</u> experimentation to determine whether a subfragment of the 1562 nucleotide promoter sequence retained promoter activity meant that a claim encompassing such fragments was not enabled:

> Applicants argue that it is highly predictable that one skilled in the art will be able to make fragments of nucleotides 156-708 of SEQ ID NO: 42 that retain fruit-associated promoter activity (response, page 7, 1st full paragraph). However, one cannot simply predict what portions of 156-1708 of SEQ ID NO: 42 would retain this activity without conducting further experimentation. **Applicants have not taught how this can be done in the absence of experimentation** (Paper No. 28, p. 6, lines 1-6, emphasis added).

However, as noted in *In re Wands*, "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to

practice the invention must not be undue experimentation. "the key word is 'undue,' not 'experimentation.'" (8 USPQ2d at1404, citing *In re Angstadt* 190 USPQ at 219)

2. Amount of direction or guidance presented. The specification provides the sequence of the promoter region of the Mel7 gene, and describes straight-forward assays for assessing promoter activity in various fruit-bearing plants (see Example 4. p. 31). Sufficient direction is provided should one skilled in the art wish to practice the invention of claim 1 using a promoter fragment from SEQ ID NO:42 that is not identical to the specific embodiment described in the working examples.

3. Presence or absence of working examples. Example 2 is a working example showing the isolation and characterization of a promoter encompassed by claims 1 and 5. Example 4 is a working example showing the fruit-associated promoter activity of this promoter in a variety of fruit species.

4. Nature of the invention. MPEP §2164.05(a) refers to the "Nature of the invention" as being the "backdrop to determine the state of the art and the level of skill possessed by one skilled in the art." The nature of Applicants' claimed invention concerns plant promoters.

5. State of the prior art. At the time of Applicants' invention, the state of the art with respect to plant promoters was high. Plant promoters were widely studied, and at the time, numerous publications were available that describe the characterization of plant promoters (e.g. see Exhibits A-E submitted with Applicants' amendment dated July 22, 2003).

6. Relative skill of those in the art. The relative skill of those in the art is high, with the ordinarily skilled person having a graduate level degree in molecular biology, or similar field. At the time of the invention, the type of experiments performed to determine whether fragments of a promoter sequence having a known promoter activity retain the same activty were routine and straight-forward to the person of ordinary skill in the art.

7. Predictability or unpredictability of the art. It is highly predictable that one skilled in the art will be able to make fragments of nucleotide 156-1708 of SEQ ID NO:42 that retain fruit-associated promtoer activity.

8. Breadth of the claims. The breadth of the claims is quite narrow. The isolated nucleic acid molecule of claim 1 comprises a promoter contained within SEQ ID NO:42 that directs fruit-associated expression of a heterologous protein. Every embodiment of the claim will contain the same promoter sequence. The only difference amongst the "species" encompassed by the claimed "genus" will be the amount of sequence flanking the minimal promoter sequence necessary for fruit-associated promoter activity.

A proper consideration of the eight factors set forth in *In re Wands* mandates a finding that Applicants claimed invention satisfies the enablement requirement set forth in 35 USC §112, 1st paragraph.

Closing remarks

For the foregoing reasons, Applicants believe that the Examiner's rejections of claims s 1, 7, 9-12, 15, and 19-23 under 35 U.S.C.§112, 1st and 2nd paragraphs, is not supported by the applicable patent law. Accordingly Applicants respectfully request that the Board reverse the Examiner's decision and allow the pending claims to issue.

Respectfully submitted,

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Appendix

1. An isolated nucleic acid molecule comprising a promoter operably linked to a heterologous protein-encoding polynucleotide sequence, wherein the promoter consists of a portion of the nucleotide sequence presented as SEQ ID NO:42 and directs fruit-associated expression of the protein in a plant cell.

7. A plant expression vector comprising the nucleic acid molecule of claim 1.

9. The plant expression vector of claim 7, wherein the polynucleotide sequence is operably linked to a control sequence, in addition to the promoter, that is recognized by a host cell transformed with the vector.

10. The plant expression vector of claim 9, wherein the polynucleotide sequence encodes *S*-adenosylmethionine hydrolase (SAMase).

11. A plant cell comprising the plant expression vector of claim 7.

12. A mature plant comprising the plant cell of claim 11.

15. A method of expressing a heterologous protein-encoding polynucleotide sequence in fruit of a transgenic plant, comprising:

(a) transforming plant cells with a plant expression vector according to claim 7;

(b) culturing said plant cells in a culturing medium containing a selection agent to select for transformed plant cells; and

(c) growing said transformed plant cells to produce a transgenic fruit-bearing plant,

wherein the heterologous protein-encoding polynucleotide sequence is expressed in fruit of said transgenic fruit-bearing plant.

19. The method according to claim 15, wherein said heterologous protein-encoding polynucleotide sequence encodes *S*-adenosylmethionine hydrolase (SAMase) and wherein said transgenic fruit-bearing plant produces mature fruit that exhibit a decrease in ethylene production relative to a non-transgenic plant.

20. A plant cell comprising the plant expression vector of claim 10.

21. The mature plant of claim12 that is fruit-bearing.

22. The mature plant of claim 21, wherein the fruit is not melon.

23. The mature plant of claim 22, wherein the fruit is selected from the group consisting of apple, pear, and tomato.